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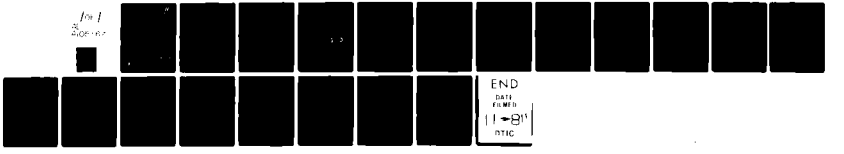

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Final Report

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The level of the sympathetic nervous system activity markedly increases during $+G_z$ acceleration stress and this increase was implicated in the etiology of cardiac subendocardial hemorrhage associated with high sustained $+G_z$ acceleration. The biochemical and physiological effect of high sustained $+G_z$ acceleration was investigated in miniature swine. The animals were chronically instrumented to measure coronary flow and left ventricular pressure. In some animals blood samples were taken from the left atrium and coronary sinus.

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cont → The results of these studies show that biochemical alteration occur in the myocardium and werepresent for up to 14 days following exposure to $+G_z$ acceleration stress. Coronary blood flow decreased at higher $+G_z$ levels while other signs of compromised coronary blood flow also were present following acceleration. Removal of portion of the sympathetic nerve system did not dramatically alter this response. These studies suggest that high sustained $+G_z$ acceleration does cause myocardial damage in miniature swine and that this injury is not reduced a great deal by alteration of the sympathetic nervous system to the heart. It is not clear what role circulating catecholamines might play in this response.

FINAL SCIENTIFIC REPORT

Grant: AFOSR-78-3506

The ability of human subjects to perform in a high acceleration environment requires that blood pressure and flow to the brain be maintained at adequate levels to support vision and cerebral function. Any limitation of cardiac function may result in a decrease in the capability of subjects to withstand the high acceleration environment common to high performance aircraft today. Evidence from many sources (Howard, 1965) suggested that at levels of acceleration stress above $+5G_z$ change in the electrocardiogram occurred that could be indicative of cardiac ischemia. Such an event could seriously limit cardiac function and result in damaging effects on the myocardium after exposure to high sustained acceleration.

Burton and MacKenzie (1976) reported that miniature swine were an excellent model for high sustained acceleration research and these investigators found that when these animals were exposed to various $+G_z$ profiles myocardial abnormalities occurred. These abnormalities were endocardial hemorrhage and some ultrastructural changes. The change in heart rate during $+G_z$ acceleration was blocked with propranolol and the amount of endocardial hemorrhage was reduced. These studies suggested as one possibility, that myocardial blood flow may be decreased during high sustained acceleration resulting in myocardial ischemia and damage.

The work encompassed by this grant was directed at measuring coronary blood flow directly and determining if both the biochemical and ultrastructural correlates were comensurate with myocardial damage in this animal model. In addition, the role of the autonomic nervous system in the cardiac response to this same environmental stress was investigated. If the autonomic nervous system to the heart was involved, it could be predicted that an exercise conditioning program

might ameliorate the effects of high sustained $+G_z$ on the heart.

METHODS

Throughout this study, adult miniature swine were used ranging in age from 9 to 18 months of age and ranging in weight from 30 to 40 kg. The animals were quarantined for 30 days prior to entry into any experimental protocol.

Most of the animals were subjected to sterile surgical procedures to implant various transducer. Anesthesia was induced first by intravenous sodium pentothol which was followed by maintenance of anesthesia using a mixture of halothane, oxygen, and nitrous oxide. The left circumflex coronary artery was carefully dissected free for about 3 cm and a Doppler ultrasonic flow probe placed around the vessel. A catheter was placed in the left atrium and in some animals a second catheter was placed in the coronary sinus through the left hemiazygous vein. In many animals, a solid state pressure transducer (Konigsberg Inst. P-6.0) was placed in the left ventricle through the apical dimple. In later studies, either the right or left stellate ganglion was removed at the time of the surgery.

Following recovery, experiments were conducted in the conscious animal both in the laboratory environment and on the human centrifuge located at USAF SAM. The laboratory studies were focused on defining the animal response to cardiac pacing, drug infusion, and exercise. The exercise regimen was designed to raise the heart rate to approxim. 200 bpm or higher. The animals were not run to exhaustion in any of the exercise studies. In some cases, animals were exercise conditioned on a motor driven treamill by running for 30 min/day, 3 times/wk for 4 wks. The centrifuge experiment at USAF SAM were conducted over a range of $+G_z$ upto a level of $+11G_z$.

In many of the animals, blood samples were obtained at the end of any particular segment and analyzed for lactate or creatine kinase activity specific

to the heart. In other studies, the animals were sacrificed immediately following exposure to a particular level of acceleration stress and the hearts rapidly removed.

The hearts removed from the animals immediately following a centrifuge experiment were analyzed for mitochondrial function and other biochemical parametres (Dowell, et al.). In most of these hearts, samples were also taken for ultrastructural analysis to determine the ultramicroscopic changes occuring with this type of stress (Lindsey et al.).

RESULTS

Coronary Blood Flow in the Conscious Anesthetized Pig

The average mean left circumflex coronary artery velocity was 25 $\pm$ 3 cm/sec with a mean resting heart rate of 84 $\pm$ 8 bpm. A change in heart rate by atrial pacing to 150 bpm increased coronary blood flow velocity by 18 $\pm$ 4 cm/sec, while left ventricular dP/dt did not change. The infusion of isoproterenol at a rate of 0.2 g/min/kg increased coronary blood flow velocity by 22 $\pm$ 3 cm/sec. Both flow velocity and dP/dt increased with rates of isoproterenol infusion below this level but only dP/dt continued to increase as the rate of infusion was increased above this level. In this group of animals, exercise increased coronary blood flow velocity by an average of 40% and heart rate by an average of 134% above control levels. Beta-adrenergic blockade (propranolol - 1 mg/kg i.v.) reduced both the coronary blood flow velocity and heart rate response to isoproterenol infusion and exercise. The elimination of most of the coronary blood flow and heart rate response to exercise by beta-adrenergic blockade would suggest that the response was primarily through sympathetic nervous system activation.

Heart Biochemical Responses in Miniature Swine Subjected to $+G_z$ Acceleration

Myocardial biochemical systems which are sensitive to hypoxic and ischemic insult were studied to determine the possible etiology of ventricular endocardial hemorrhage following $+G_z$ stress. The animals were exposed to a single exposure to $+9G_z$ for 120 sec. Approximately 1-2 hrs following $+G_z$ exposure, the animals were anesthetized and the hearts removed for analysis. Acceleration exposure resulted in a loss of acid phosphatase enzyme from the membrane-bound lysosomal fraction with concomitant increased activity in the soluble fraction. These data suggested that lysosomal membrane integrity had been disrupted. Mitochondrial preparations from $+G_z$ stressed hearts exhibited marked increases in active respiratory rate and rate of calcium transport while oxidative phosphorylation efficiency was unchanged. These results clearly indicate that $+G_z$ acceleration is capable of altering myocardial biochemical systems but the alterations in cellular processes may be mediated by influences other than hypoxia or ischemia.

Coronary Flow and Myocardial Responses to High Sustained $+G_z$ Acceleration

The miniature swine seemed to tolerate the exposure to the various levels of acceleration used in this study. The peak levels of acceleration were randomized for each animal so as to minimize the effect of the first exposure level on the subsequent results. At 9 $+G_z$, all of the animals appeared to remain conscious. The criterion for this was the kicking and grunting behavior of the animal. Closed circuit television allowed the observer to watch and hear the animal during the various profiles. At most of the high acceleration levels (+7 and +9), some degree of bradycardia was noted. The severity of this bradycardia varied greatly between animals. All of the measured parameters were allowed to return to control values prior to any succeeding runs.

After the animal had been placed on the centrifuge and before each level of acceleration, control values were taken for heart rate, left ventricular systolic and diastolic pressure, left circumflex coronary flow, and the maximum rate of rise of left ventricular pressure. The maximum rate of rise of the left ventricular pressure was used as an index of the contractile state of the myocardium. The average values with one standard error of the mean were found to be: HR, 97 $\pm$ 3 bpm; LV systolic pressure, 156 $\pm$ 8 mm Hg; LV diastolic pressure, 4 $\pm$ 1 mm Hg; LCCF, 58 $\pm$ 5 cc/min; and, $\dot{P}$, 2472 $\pm$ 164 mm Hg/sec.

The results of exposure to 3, 5, 7, and 9 $+G_z$ acceleration for various periods of time can be seen in Table 1. The average heart rate increased with acceleration, but the magnitude of increase became less with successive increases in the level of $+G_z$ acceleration. At the point of measurement, the left ventricular systolic pressure increased, but it must be noticed that this was not a transmural pressure. Coronary flow decreased at all levels of acceleration studied. There did seem to be a tendency for coronary flow to increase during individual acceleration profiles but in most of the studies remained below control values. The contractile index of the left ventricle increased with acceleration. The increase seemed to be less with higher levels of acceleration. At time, there appeared to be waves in the coronary flow that coincided with changes in heart rate.

Ultrastructural Effects of $+G_z$ Stress or Swine Cardiac Muscle

The animals used in this study were subjected to $+9G_z$ acceleration of either 60 or 120 sec. Within 2 hrs following the $+G_z$ acceleration profile, the anterior papillary muscle was removed and prepared for scanning and electron microscopy. Ultrastructural changes observed in the cardiac myocytes induced cellular redistribution of mitochondria and nuclei. Tears in the contractile fibers, bizarre profiles or nuclei, and peculiar membrane-bound bodies in the cytoplasm also were

observed. Hemorrhagic areas were localized around the Purkinje fibers. The T-system and plasma membrane appeared unperturbed. These studies indicated that exposure to high sustained $+G_z$ resulted in damage to the myocardial ultrastructure.

Heart Biochemical Responses 14 Days After $+G_z$ Acceleration

The animals used in this study were subjected to an acceleration profile encompassing 3, 5, 7, 9, and 11 $+G_z$ for 60-120 sec at each acceleration level. Fourteen days after the $+G_z$ exposure, free lysosomal enzyme activity was determined as given previously. The free lysosomal enzyme activity was reduced by 15-40% in both the epicardial and endocardial portions of the left ventricle while bound enzyme activity remained near control levels. Since free lysosomal enzyme activity was previously found to be elevated approximately two-fold in response to a single $+9G_z$ acceleration exposure, the responses found 14 days after these $+G_z$ acceleration profiles would be consistent with a myocardial damage-repair mechanism. The DNA levels in the left ventricle of the $+G_z$ stressed animals were significantly lower than control values, while the RNA/DNA ratio was markedly elevated. The nucleic acid results imply a metabolic hyperfunction of the remaining nuclear material.

Specificity of Myocardial Responses to High-Sustained $+G_z$ Acceleration

The above studies have shown biochemical and ultrastructural alterations in hearts of miniature swine after $+G_z$ acceleration exposure. These alterations suggested that ischemic or hypoxic myocardial insult could have resulted from $+G_z$ stress. Physiological and biochemical data were obtained from another group of chronically instrumented animals and were consistent with this hypothesis, since a) left circumflex coronary artery blood flow velocity was not appropriately augmented, and b) a net myocardial lactate production was observed during 9-11

$+G_z$ acceleration stress. However, the possibility existed that the above results represented a non-specific stress exposure in the miniature swine which would be coupled with an increase in the level of circulating catecholamines. This possibility was evaluated in another group of animals exposed to the stress of treadmill exercise. The exercise intensity was sufficient to elicit increased heart rate similar to that seen during $+G_z$ acceleration (heart rates up to 240 bpm). In contrast to $+G_z$ acceleration, left circumflex coronary blood flow velocity was dramatically augmented (210 $\pm$ 30% above resting values) and a net myocardial lactate utilization was present during exercise. These results clearly indicate that the myocardial responses previously observed during and after high-sustained $+G_z$ exposure were specific to acceleration stress.

Effects of Exercise Conditioning on the Physiological Responses to Acceleration Stress

The physiological and biochemical results in exercise stressed miniature swine show that distinct differences exist between the overall myocardial responses resulting from exercise stress and those resulting from $+G_z$ acceleration stress. In response to exercise, coronary blood flow is appropriately augmented in response to the elevated myocardial metabolic requirements established by increases in both heart rate and contractility which accompanies exercise. No evidence was obtained which would indicate relative myocardial ischemia during either acute exercise or acute exercise following exercise conditioning. Therefore, a generalized stress response does not appear a likely explanation for the biochemical and morphological alterations previously observed in acceleration stressed miniature swine. Exercise conditioned animals were subjected to $+G_z$ acceleration stress at USAF SAM and no significant differences were found as compared to the unconditioned animals. Heart rate tended to be reduced at each acceleration level studied and coronary blood flow velocity tended to be higher

but as stated these differences were not significant. Thus, it appears that exercise conditioning does not alter the response of this animal specie to acceleration stress.

Biochemical Effects of Repeated Exposure to Acceleration

In conjunction with Dr. John Burns at USAF SAM, left ventricular tissue samples were obtained from miniature swine which had been exposed to multiple simulated combat maneuvers for time periods of 1 day to 6 months. Tissue levels of protein, nucleic acids, connective tissue, and selected aerobic and anaerobic enzymes were measured. The most striking results from these studies were a marked increase in connective tissue within the left ventricle of animals which had been exposed to simulated combat maneuvers for 1 month. Unfortunately, the tissue sampling site was changed for the 6-month animals and results from these experiments were equivocal.

Right and Left Stellate Ganglionectomy and the Response to Exercise and Acceleration Stress

Twelve adult miniature swine were used in this study. The animals were instrumented to measure left ventricular pressure, left circumflex coronary flow velocity, heart rate, and in some instances arterial and coronary sinus difference in oxygen content. In 4 of the animals, the right stellate ganglion was removed (RSG_X) and in 5 animals the left stellate ganglion was removed (LSG_X) at the time of surgery. Following recovery, the animals were subjected to a standardized exercise protocol and subsequently exposed to various acceleration levels at USAF SAM. At the termination of the experiments, the animals were sacrificed and the hearts examined for any microscopic changes.

The data obtained during the standardized exercise test in the 12 animals can be seen in Table II.

Removal of the right or left stellate ganglion did not compromise the ability of the animals to respond to the exercise stress. LSG_X resulted in a higher heart rate while RSG_X resulted in lower heart rate compared to control animals. Contractility of the ventricle was reduced by LSG_X but not by RSG_X. Coronary blood flow velocity was not greatly changed. During acceleration stress similar changes were observed in each group of animals but no differences were found with gross microscopic observation of the hearts. These data indicate that removal of portions of the autonomic nervous system did not compromise the cardiac response to exercise or acceleration stress.

The post-ganglionic sympathetic nerves to the heart arise from either the right or the left stellate ganglion. Anatomically, the stellate ganglion is a fusion of the superior thoracic and inferior cervical ganglion in most mammals. Several investigators have adequately demonstrated that the left ganglion sends fibers that course mainly over the left side of the heart with a small representation on the right side of the heart. Stimulation of the various post-ganglionic nerves from the left ganglion result in an increase in contractile force of the left ventricle with some effect on the right ventricle but very little effect on heart rate. The post-ganglionic fiber from the right stellate ganglion course over the right side of the heart and do have some representation on the left side of the heart. Stimulation of these nerves results in an increase in contractile force of the right ventricle and increases in heart rate. In certain regions of the left ventricle contractile force can also be increased. Removal of the left stellate ganglion (LSG_X) in dogs has been shown to result in little effect on the response to submaximal exercise. The basic goals of the present study was to determine if the same was true in the miniature swine and in addition, if the removal of the ganglion would result in a deterioration of the cardiac response to acceleration stress. Previous studies have also indicated that a tonic sympathetic vasoconstrictor tone on the coronary vessels was removed

by LSG_x. This alone would give some idea about the role of the autonomic nervous system in the myocardial hypoxic response to acceleration stress. In the two groups of animals, one group was subjected to bouts of submaximal exercise for the next 8 wks, while the second group was subjected to 30 min of exercise 3 times/wk for 8 wks. At the end of this period the animals were transported to USAF SAM and exposed to various levels of acceleration stress. All animals were exposed to levels of acceleration of +3, +5, +7, and $+9G_z$. ECG electrodes were placed on all four limbs. Blood samples were drawn during exercise and at the end of the various acceleration levels. At the termination of acceleration study, the animals were sacrificed and the hearts rapidly removed for microscopic inspection and tissue sampling. The blood and tissue samples were analyzed for CPK and LDH isoenzymes after return to the University of Oklahoma HSC.

During the exercise studies, average heart rate increased from 85 $\pm$ 10 bpm to 270 $\pm$ 8 bpm at the highest level of exercise used in these studies. There was no significant difference from a comparison with control animals. Resting coronary blood flow velocity was 26 $\pm$ 5 cm/sec and increased to 63 $\pm$ 8 cm/sec at the highest level of exercise. This value of coronary blood flow velocity was not significant but was higher than that observed in control animals. Left ventricular pressure and the maximum rate of rise of left ventricular pressure ($\dot{P}_{max}$) increased during exercise. $\dot{P}_{max}$ increased by 80 $\pm$ 9% during the exercise regimen. Coronary sinus oxygen saturation decreased with exercise going from an average value of 47 $\pm$ 9% to 25 $\pm$ 7% at the highest level of exercise attained. In the animals in which both arterial and coronary sinus blood samples were obtained there was always a negative lactate across the heart. This means that the heart was well perfused and lactate was being taken up by the tissue. No evidence of changes in CPK-MB were found during or after exercise.

Acceleration studies of LSG_X miniature swine and LSG_X conditioned miniature swine.

As outlined above, both groups of animals were exposed to various acceleration profiles and then sacrificed. In the group that was LSG_X only, heart rate and $\dot{P}_{max}$ increased at the lower levels of acceleration but at about $+7G_X$ a bradycardia usually occured with $\dot{P}_{max}$ still elevated. CBF increased at all levels of acceleration up to $+7G_X$ when the increase was not as great as that found at the lower levels of acceleration. However, it must be emphasized that CBF did increase. Heart rate increased from a resting value of 90 $\pm$ 8 bpm to a maximum value of 240 bpm + 10 bpm at most acceleration levels. When the bradycardia occurred, heart rate would generally fall below the resting value. Resting CBF average 28 $\pm$ 6 cm/sec and increased to a high value of 48 $\pm$ 5 cm/sec during the various levels of acceleration. Left ventricular systolic and diastolic pressure increased according to the level of acceleration. $\dot{P}_{max}$ always increased from a resting value of 3560 $\pm$ 543 mm Hg/sec to a maximum value of 5340 $\pm$ 980 mm Hg/sec during acceleration. Lactate increased in the coronary sinus blood above that found in the arterial blood sample. A small increase in plasma CPK-MB was also found. At the higher $+G_X$ levels, a reactive hyperemic coronary flow response was always observed upon cessation of the acceleration force.

These results clearly indicate that the cardiac and coronary response to acceleration was different from that found during submaximal exercise in these animals. Maximum heart rates were similar as was the increase in $\dot{P}_{max}$, yet the CBF response was greatly diminished. The increase in coronary sinus lactate and the reactive hyperemic response indicated that some type of restriction of coronary flow and tissue hypoxia had occurred. Despite the removal of the LSG, subendocardial hemorrhage was found in all of these animals. This was a very puzzling fact unless the mechanical forces were responsible for the results. In the LSG_X dog, cardiac tissue catecholamine levels were reduced by 50% and no

increase in sensitivity to circulating catecholamines could be found. If the same was true in the swine, the results could not be explained by a mechanism of supersensitivity. The distribution of coronary flow as measured by radioactive microspheres indicate that the distribution across the myocardial wall was similar during acceleration stress at the $+5G_z$ as compared to control. This may not be suprising since CBF increased by the greatest amount at this level, yet evidence of ischemia was still found. Normal distribution in these studies does not indicate that flow to all areas was the same as during the control period.

In the group of animals that were LSG_x and exercise conditioned the response pattern was almost identical to that described above. No consistent difference could be found between the two groups of animals. Upon sacrifice, the amount of endocardial hemorrhage was definitely less in this group as compared to the previous group of animals. Thus, it appears that exercise conditioning in some way may ameliorate the effect of acceleration stress.

The results of these studies clearly indicate that the autonomic nervous system does play a significant role in the response to acceleration stress and may be responsible in part for the subendocardial hemorrhage seen in previous studies. Release of norepinephrine in high concentration locally could cause vasoconstriction of blood vessels during acceleration stress and upon return to normal gravity the increase in pressure could cause vessels to expand rapidly. The rapid expansion may result in leakage of red blood cells into the extravascular space and possibly rupture of small vessels. As stated, the latter idea is only speculation and must be proven before acceptance.

SIGNIFICANT ACCOMPLISHMENTS

The underlying premise in these studies was that the endocardial hemorrhage was due to a tissue ischemia or hypoxia and not due to some mechanical factors or circulating catecholamines. This premise does not exclude the potential for a contribution of these factors but does not view them as the initiating events. From this perspective the following points can be made about the studies conducted during the course of this grant. These are listed below:

1. Coronary blood flow to the left ventricular myocardium decreases with increasing levels of $+G_z$. At levels of $+9G_z$, some clear cut evidence was obtained to suggest myocardial ischemia.
2. Myocardial ischemia was strongly suggested by the reactive hyperemia in flow when the acceleration profile was terminated and by the production of lactate and myocardial creatine kinase. Use of an anti-G device tended to reduce these effects of acceleration.
3. The ultrastructural changes observed in this study are consistent with the conclusion of myocardial injury with high sustained acceleration in this experimental model.
4. Exercise conditioning did not ameliorate the effects of acceleration stress to any significant degree. This is not very surprising, since others have reported similar results in human volunteer subjects.
5. Removal of the left stellate ganglion did not alter the degree of endocardial hemorrhage in these animals but did augment the coronary flow response to acceleration stress. Thus, the left stellate ganglion appears to limit coronary blood flow under these conditions of stress.
6. Right stellate ganglion removal altered the heart rate response to acceleration stress but did not change any of the other parameters studied.

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TABLE I

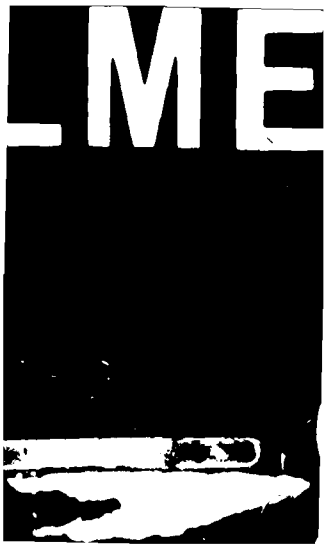
The average values for heart rate (HR), left ventricular pressure (LVP), the maximum derivative of left ventricular pressure ($\dot{P}$), and the mean left circumflex coronary flow (LCCF) expressed as the percent of the absolute control values in response to $+G_z$ acceleration. The values were taken at the indicated times after reaching peak acceleration levels. The numbers in parentheses are $\pm$ one standard error of the mean.

G	T(sec)	H.R.	LVP		LCCF	$\dot{P}$
			Systolic	Diastolic		
3	60	202 (22)	138 (23)	64 (15)	77 (27)	172 (20)
	120	219 (25)	146 (33)	53 (21)	53 (14)	126 (4)
5	30	217 (21)	151 (27)	50 (20)	58 (18)	170 (22)
	60	169 (25)	151 (23)	62 (20)	60 (18)	140 (12)
7	30	148 (22)	173 (22)	127 (9)	80 (22)	144 (13)
	60	167 (29)	152 (20)	101 (14)	54 (9)	112 (16)
9	30	145 (21)	146 (45)	77 (19)	78 (26)	116 (11)
	60	93(24)	145 (70)	136 (36)	85 (27)	120 (26)

TABLE II

Average values of the maximum rate of rise of left ventricular pressure (dP/dt_{max}), heart rate, and left circumflex flow velocity (LCV) in 12 miniature swine. See text for further details.

Condition	dP/dt max (mm Hg/sec)	Heart Rate (bpm)	LCV (cm/sec)
Intact Control	2852 ± 326	105 ± 16	18 ± 1
LSG_x Control	2677 ± 319	96 ± 4	19 ± 3
RSG_x Control	3526 ± 249	90 ± 4	20 ± 2
Intact 4.8 kph/12%	7750 ± 250	254 ± 8	42 ± 2
LSG_x 4.8 kph/12%	6169 + 1308	260 + 7	45 ± 5
RSG_x 4.8 kph/12%	7660 ± 870	240 ± 5	46 ± 3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